UBX1325, a small molecule inhibitor of Bcl-xL, attenuates vascular dysfunction in two animal models of retinopathy

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Introduction

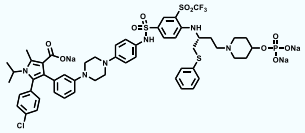
Retinal vasculopathies account for the primary causes of loss of sight in the industrialized world and current standards do not fully address these diseases. Focused on novel treatment paradigms, we developed UBX1325, a novel small molecule inhibitor prodrug of specific subtypes within the B-cell lymphoma 2 (Bcl-2) family of apoptosis regulatory proteins and assessed its efficacy in senescence-associated models of retinopathy[1].

Methods

- Target engagement (TE), decreased Bcl-xL:Bim or Bcl-2:Bim complexes, was measured by an electro-chemiluminescence-based assay in cell or retinal lysates from C57BL/6 mice after intravitreal (IVT) injection of UBX1325.
- Senolysis was measured as cell viability (CellTiter-Glo) after 72h incubation of senescent HRMEC with the UBX1325 parent.
- Initiation of apoptosis (mechanism engagement, ME) was measured by caspase-3/7 activation.
- Adult mice and neonatal mice from oxygen induced retinopathy (OIR; 75% O_2 from post-natal day (P)7-P12) or normoxic controls were used for TE and ME after IVT injection of UBX1325 at P12.
- Vascular endpoints (neovascular and avascular area) were evaluated at P17 by isolectin B4 staining in OIR mice given a single IVT injection of UBX1325 at P12.
- UBX1325 was studied in the streptozotocin (STZ)-induced retinopathy model. UBX1325 was injected IVT at weeks 8 and 9 post-STZ, and retinal endpoints were measured at week 10. Vascular leakage was evaluated by Evans blue dye extravasation into the retina after intravenous injection. The dark-adapted electroretinogram was used to assess retinal function with increasing flash intensity.

Results

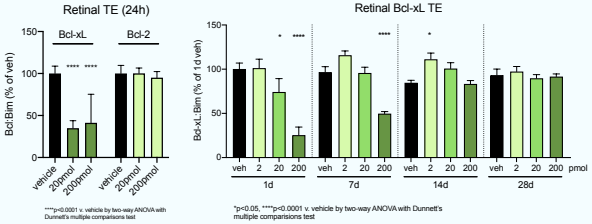
UBX1325 is a Bcl-xL inhibitor prodrug

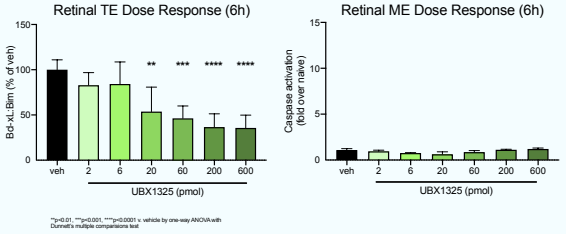


	HRMEC TE (pIC_{50}) (95% CI)	HRMEC ME (pEC_{50}) (95% CI)	HRMEC senolysis (pEC_{50}) (± SD)
UBX1325 parent	**8.1** (7.8, 8.6)	**7.3** (∞, 8.2)	**7.8** (±0.6)

IVT UBX1325 leads to a reduction of anti-apoptotic Bcl-xL:Bim complexes in the adult mouse retina

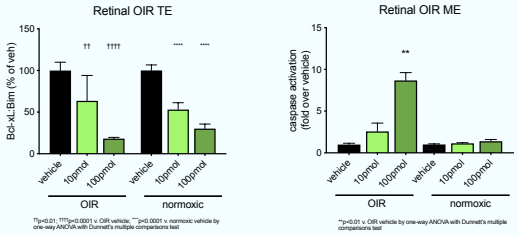
- IVT injection of UBX1325 results in selective inhibition of Bcl-xL in the mouse retina
- A single IVT administration of UBX1325 results in dose- and time-dependent inhibition of Bcl-xL
- Bcl-xL inhibition does not induce apoptosis in a healthy adult mouse retina





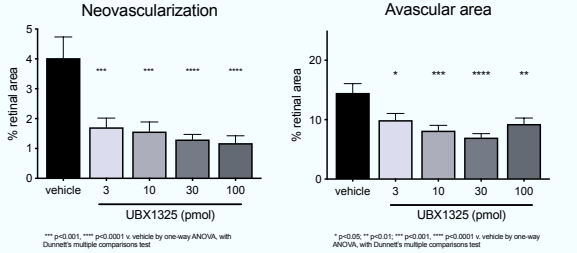
IVT UBX1325 promotes apoptosis in OIR, but not normoxic mice

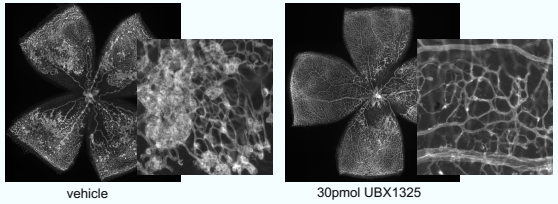
- IVT injection of UBX1325 results in 24h Bcl-xL TE (37-81%) in OIR and normoxic animals
- Selective caspase-3/7 activation was observed (3-9-fold) in OIR animals 24h after IVT administration of UBX1325



UBX1325 improves retinal vascular phenotypes in the mouse OIR model

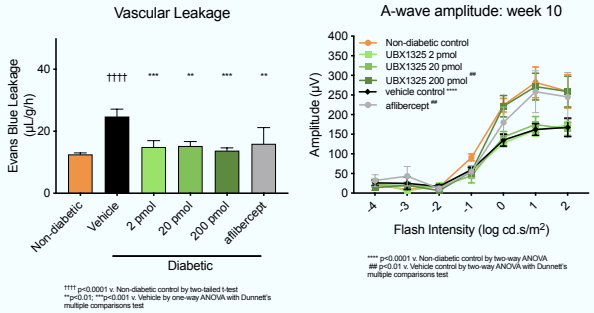
- IVT injection of UBX1325 improves both retinal neovascularization (58-71%) and avascular area (32-52%)





UBX1325 reduces vascular leakage and improves retinal function in the diabetic mouse

- IVT injection of UBX1325 reduced retinal vascular permeability (78-90%) and improved ERG (a- and b-wave amplitude)



Conclusions

Inhibition of retinal Bcl-xL by UBX1325 promotes apoptosis in the senescence-associated OIR model. Although anti-VEGF agents decrease neovascularization in OIR[2], UBX1325 is differentiated as it improves both the retinal neovascular and avascular areas in the OIR model. UBX1325 also improves vascular leak and ERG in STZ mice. Collectively, our data support development of UBX1325 for retinal vasculopathies and initial clinical evaluation in patients with diabetic macular edema (DME)[3].

[1]**Pathological angiogenesis in retinopathy engages cellular senescence and is amenable to therapeutic elimination via BCL-xL inhibition** (2021). S Crespo-Garcia, PR Tsuruda, A Dejda, RD Ryan, F Fournier, SY Chaney, F Pilon, T Dogan, G Cagnone, P Patel, M Buscarlet, S Dasgupta, G Girouard, SR Rao, AM Wilson, R O'Brien, R Juneau, V Guber, A Dubrac, C Beausejour, S Armstrong, FA Mallette, CB Yohn, J-S Joyal, D Marques, PJ Beltran, P Sapieha. 33(4): 818-832

[2]**Senescence-associated secretory phenotype contributes to pathological angiogenesis in retinopathy** (2016). M Oubaha, K Miloudi, A Dejda, V Guber, G Mawambo, M-A Germain, G Bourdel, N Popovic, FA Rezende, RJ Kaufman, FA Mallette, P Sapieha. 8(362): 362ra144

[3]**Safety and Tolerability Study of UBX1325 in Patients With Diabetic Macular Edema or Neovascular Age-Related Macular Degeneration.** UNITY Biotechnology. NCT04537884